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Cancer, fertility and pregnancy: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

The estimated incidence of cancer diagnosed in pregnant women in developed societies is 1:1000 pregnancies and is predicted to rise as childbearing is shifted towards the late reproductive age. The most common cancers associated with pregnancy are cervical, breast cancer, melanoma, lymphomas and acute leukemias (Table 1).

diagnosis and staging

The diagnostic work-up should include a thorough physical examination, including the pelvis, breasts, lymph nodes, skin and should limit unnecessary exposure to ionizing radiation. Fine needle aspiration, core needle or open excisional biopsies are safe to perform. Chest X-ray and mammography with abdominal shielding and ultrasonic examinations are the cornerstone of a basic staging, supplemented by MRI scans in the second/third trimesters when needed [IV, B]. In view of the theoretical risk of fetal heating/cavitation, first trimester MRI scans should be done sparingly and the potentially teratogenic gadolinium should not be administered [V, D]. Computerized tomography or radioisotope studies should be avoided. Minor staging procedures (spinal tap, bone marrow biopsy, endoscopies) are relatively safe to perform [IV, B].

risk assessment

Ionizing radiation and cytotoxic agents have potential mutagenic, teratogenic and carcinogenic effects for the embryo, depending on dose, nature of compound, treatment field and gestational stage (Table 2).

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Fetal exposure to radiation doses in excess of 5–10 cGy should be avoided. This threshold dose is associated with a very low risk of stochastic biologic effects (mutations) and does not cause non-stochastic effects (malformations, developmental disorders). Exposure to antineoplastic agents should be avoided during the first trimester (organogenesis).

treatment and follow-up

The optimal therapeutic strategy should be jointly chosen by the medical team, patient and family and will depend on gestational age, nature and stage of cancer, treatment options and patient wishes. The medical team should include an obstetrician, a neonatologist, a medical oncologist, a surgeon and a psychologist and the patient should be treated at major hospitals with the required expertise and infrastructure.

Pregnancy termination is advised in the case of chemotherapy or radiotherapy administration during the first trimester, need for radical gynecologic surgery, poor maternal life expectancy.

cytotoxic chemotherapy

Chemotherapy can be administered during the second and third trimesters with reasonable safety, though there is an increased risk of still birth, growth retardation and premature delivery [III, B]. Older-generation alkylators (thiotepa, busulfan, chlorambucil, nitrogen mustard) and antimetabolites (aminopterin, methotrexate) have the most pronounced teratogenic and abortive potential, while anthracyclines, 5-fluorouracil, cytarabine and vinca alkaloids the least. Emerging evidence from a small number of case reports suggests that taxanes and platinum compounds are relatively safe to administer beyond the first gestational trimester [IV, C]. There are no data on pemetrexed, gemcitabine, vinorelbine.

targeted agents

Only a few pregnant women have inadvertently been exposed to targeted agents. Trastuzumab caused oligohydramnios in four and abnormal implantation in one out of seven pregnant women, while rituximab only caused transient neonatal

lymphopenia in four reported cases. Imatinib was occasionally associated with low birth weight and premature delivery in 29 reported cases, though one case of hypospadias and one of meningocele have been published as well. In view of lack of data and past experience with the antiangiogenic agent thalidomide, administration of targeted agents modulating angiogenesis (bevacizumab, sunitinib, sorafenib) should be avoided in pregnant women [V, D].

surgery, radiation therapy and timing of delivery

Delivery should take place after weeks 32–35, 3 weeks after the last chemotherapy cycle. Surgical operations can be safely performed during the first two trimesters, with a slight to moderate increase in the risk of abortion during the first trimester, especially with abdominal operations. In the third trimester, operation or deferral after delivery may be chosen according to circumstances [IV, B]. Radiotherapy should be administered post-partum and care should be taken to avoid fetal exposure to ionizing irradiation of any source to <5–10 cGy [IV, C].

supportive therapy

Antiemetics (ondansetron, metoclopramide, meclozine) may be safely administered with ommittance of corticosteroids in the first trimester [II, B]. Analgesics (paracetamol, opioids, anti-inflammatory agents) [IV, B] and growth cytokines [V, D] have been administered in pregnant women beyond the first trimester without untoward effects, though some risk of fetal respiratory depression and ductus arteriosus closure exists. Biphosphonates and tamoxifen, aromatase inhibitors, somatostatin should be deferred after delivery. Breast feeding should be avoided during chemotherapy.

Although placental/fetal metastases are exceedingly rare, histological examination of the placenta after delivery should take place.

Table 1. Incidence of tumor types in pregnant women

Malignancy	Incidence (per no. of gestations)
Malignant melanoma	1:1000–10 000
Breast carcinoma	1:3000–1:10 000
Carcinoma of the cervix	1:2000–10 000
Lymphoma	1:1000–1:6000
Leukemia	1:75 000–1:100 000
Ovarian carcinoma	1:10 000–1:100 000
Colon cancer	1:13 000

follow-up

The follow-up of women diagnosed with cancer during pregnancy and their offspring should adhere to common standards. Most cohort studies showed that the outcome of pregnant cancer patients is not significantly inferior to non-pregnant patients matched for age and stage of cancer, though some series reported inferior survival of pregnant women with cancer. Still, it is currently unknown whether the latter finding is due to more aggressive cancer biology during gestation or simply due to undertreatment of these patients.

There is no evidence to establish that patient outcome is compromised by future pregnancies [III, B]. Most cohort studies have shown that women with a history of breast cancer who later become pregnant are at a reduced risk of malignant relapse/death. This finding should be interpreted with caution, as healthy women are the ones who attempt pregnancy, while those who experience a malignant relapse do not.

To date, there is no evidence establishing that *in utero* exposure to chemotherapy (beyond the first trimester) or radiotherapy (doses <10–20 cGy) compromises the long-term physical and mental development of children [IV, B].

Most oncologists would recommend that potentially cured breast cancer patients postpone childbearing for at least 2–3 years, the median time to recurrence for relapsing women.

fertility preservation

The gonadotoxic effects of ionizing radiation, chemotherapy and surgery depend on patient age, treatment fields, total dose and nature of insulting agents (Table 3).

Conservative or modified abdominopelvic/genitourinary surgery should only be implemented if it does not compromise patient outcome. All patients at risk for infertility who have not completed childbearing should discuss germ cell storage options with the medical team.

Available interventions for male fertility preservation are unlikely to delay cancer treatment. Semen cryopreservation of at least three samples with 48-h abstinence intervals is recommended for men [III, A]. For azoospermic men, testicular sperm extraction may be an option for fertility preservation [V, D]. Prepubertal males may participate in clinical research of testicular tissue/spermatogonial stem cell storage. No studies support the effectiveness of male gonadal protection by means of hormonal manipulations during chemotherapy or radiotherapy.

Female fertility preservation procedures have requirements for scheduling and ovarian stimulation, resulting in a likely

Table 2. Gestational stage and effects of antineoplastic therapy

Gestational stage	Embryonal/fetal development	Impact
Weeks 0–2	Undifferentiated multicellular organism	'All or nothing', spontaneous abortion or normal development
Weeks 3–12	Organogenesis	Spontaneous abortion, major congenital anomalies
2nd and 3rd trimesters	Intrauterine growth and maturation, continuing development of CNS, gonads, teeth–palate, eyes, ears	Functional defects and minor anomalies of late-forming tissues, still birth, intrauterine growth retardation, premature delivery, myelosuppression

Table 3. Risk of female gonadotoxicity of various antineoplastic agents

	High risk (>80%)[a]	Intermediate risk	Low risk (<20%)	Unknown risk
Single agents	Cyclophosphamide	Anthracyclines	Methotrexate	Taxanes
	Busulfan	Cisplatin	Bleomycin	Oxaliplatin
	Melphalan	Carboplatin	5-Fluorouracil	Irinotecan
	Chlorambucil	Ara-C	Actinomycin-D	Monoclonal antibodies
	Dacarbazine		Vinca alkaloids	Tyrosine kinase inhibitors
	Procarbazine		Mercaptopurine	
	Ifosfamide		Etoposide	
	Thiotepa		Fludarabine	
Combinations and radiation therapy	Nitrogen mustard			
	High-dose cyclophosphamide/ busulfan and hematopoietic stem cell transplantation	CMF, CAF, FEC × 6 in women 30–39 years	ABVD.CMF, FEC, CAF × 6 in women <30 years	
	Ovarian irradiation	AC, EC × 4 in women >40 years	CHOP, CVP	
	CMF, CAF, FEC × 6 in women >40 years		Protocols for AML, ALL	
			AC × 4 in women <40 years	

[a]Incidence of permanent amenorrhea in exposed women.

delay of 2–6 weeks of cancer treatment initiation. Embryo cryopreservation and ovary transposition are the only established fertility preservation options for female patients, live birth rates being inferior to fresh embryo procedures. Menstrual function resumes in ∼50% of women undergoing ovarian transposition, due to ischemia and scatter radiation [III, A]. Short-term ovarian stimulation with gonadotrophins is necessary for oocyte retrieval and may be associated with a theoretical risk of growth of hormone-sensitive tumors. Emerging evidence on alternative (letrozole or tamoxifen) stimulation protocols is scant. Experimental fertility preservation options are oocyte cryopreservation for women without a partner and ovarian tissue storage for those who cannot undergo ovarian stimulation or are prepubertal. Despite >120 deliveries with oocyte storage, issues with oocyte damage, DNA integrity and low yield of pregnancy urge us to consider oocyte cryopreservation experimental. Ovarian tissue reimplantation carries a low risk of reintroduction of cancer cells if ovarian micrometastases were present.

Female gonadal protection from chemotherapy by means of oral contraceptive or GnRH agonist administration was effective in observational studies but should be considered investigational until results of ongoing prospective randomized trials become available [III, B].

Post-hoc subgroup analyses of prospective trials and three meta-analyses showed that amenorrhea induced by chemotherapy or GnRH-agonists, compared with menses preservation, was associated with improved survival in premenopausal women with resected hormone receptor-positive breast cancer. However, permanent amenorrhea had no advantage over a temporary one in terms of patient outcome. Theses facts should be communicated to the patient with hormone-responsive tumor who is considering preservation of menses.

Aside from the risk of cancer relapse which may require avoidance of childbearing for 2–3 years, all male and female patients who remain fertile after cancer treatment should defer childbearing for at least 12 months to ensure germ cell integrity [IV, C].

Women with a history of cancer/cancer treatment should be considered high risk for perinatal complications (maternal cardiac failure, miscarriage, low birth weight and prematurity of the newborn) and receive specialized, close care. Though poor DNA integrity has been reported in gametes of cancer patients, in the setting of successful fertility preservation/ restoration there is no evidence that prior history of cancer or cancer therapy increases the rates of malformations, functional defects or malignancies in the patient's offspring [V, D].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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